

Hyperthyroidism and Liver Dysfunction: A Review of a Common Comorbidity

Ernest Yorke

Department of Medicine & Therapeutics, University of Ghana Medical School, Accra, Ghana.

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ABSTRACT: Deranged liver enzymes due to hyperthyroidism rather than intrinsic liver pathology are not uncommon. The reported prevalence of liver biochemical abnormalities in patients with untreated thyrotoxicosis varies widely ranging from 15% to 76%. The suggested causes of liver dysfunction include direct hepatocyte injury, co-morbid heart failure, associated autoimmune conditions (especially in the setting of Graves' Disease), preexisting liver disease and drugs including antithyroid medications. Although, some patients may have a pattern of mild liver injury, about 1% to 2% can have fulminant hepatitis. Liver enzymes can return to normalcy in as many as 77% to 83% of patients once the initiations of thionamides are started in a timely fashion, which can help forestall complications and prevent or minimize multi-organ dysfunction. Clinicians should maintain a high index of suspicion for underlying hyperthyroidism in patients presenting with unexplained liver dysfunction or unexplained jaundice.

KEYWORDS: Hyperthyroidism, liver dysfunction, liver enzymes

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CORRESPONDING AUTHOR: Ernest Yorke, Department of Medicine & Therapeutics, College of Health Sciences, University of Ghana Medical School, Accra, Ghana. P.O. Box KB796, Korle-Bu, Accra. Emails: pavlovium@yahoo.com; eyorke@ug.edu.gh

Introduction

Hyperthyroidism impacts multiple systems of the body such as the nervous, cardiovascular and gastrointestinal systems, with the liver being an important organ affected in the latter.¹ Hyperthyroidism disproportionately affects women rather than men (5:1) and appears to be common among smokers.^{2,3} The overall incidence of hyperthyroidism is estimated to be about 0.05% to 1.3 % with a predominant number being subclinical, this figure rises to between 4% and 5 % among older women.³

Aside other abnormalities,⁴ liver biochemical dysfunctions are found in between 15% and 79% of untreated hyperthyroidism patients with some suffering from severe liver damage of failure and impaired synthetic function.^{5,6} In a recently published systematic review and meta-analysis by Scappaticcio et al,⁷ between 55% and 60% of patients with untreated hyperthyroidism had at least one abnormal liver function test. The prevalence of abnormal liver function tests with respect to alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total bilirubin (BIL), and γ -glutamyltransferase (GGT) among the hyperthyroid patients were 33%, 23%, 44%, 12%, and 24% respectively.

The liver and thyroid hormones interact at multiple levels to maintain homeostasis. The two biologically active thyroid hormones: thyroxine (T₄) and 3,5,3',5'-tetraiodo-L-thyronine (T₃) are synthesized solely in the thyroid gland in the case of the former and both thyroid gland and other tissues in the latter.^{8,9} Approximately 80% of T₃ is formed by 5'-deiodination of T₄ in extrathyroidal tissue: commonly the liver and kidney and rapidly degraded by deiodination at a rate of approximately 75% per day.^{8,9} The production rate of T₄ is 80 to 100 mcg per day, all of which is produced in the thyroid gland and is degraded at a rate of 10% per day. Approximately 80% is

deiodinated: 40% to form T₃ and 40% to form reverse T₃ (rT₃). The remaining 20% is conjugated with glucuronide and sulfate, deaminated and decarboxylated to form tetraiodothyroacetic acid (tetrac) in the liver.^{8,9}

Over 99% of T₄ and T₃ in serum are bound to serum proteins, thyroxine-binding globulin (TBG), transthyretin, albumin and lipoproteins which are mainly produced in the liver. These aids to maintain the serum free thyroid hormones within narrow limits yet ensure immediate and continuous availability to tissues. It is the serum-free T₄ and T₃ concentrations that determine the hormones biological activity.^{8,9}

The liver requires adequate amounts of thyroid hormones to execute its metabolic functions optimally. Thyroid hormones, through regulating the levels of ligandin, an anion-binding protein, affect the enzymatic activity of glucuronyltransferase which helps in maintaining the metabolism of bilirubin.¹⁰

Among patients with preexisting liver disease, the liver dysfunction may be as a result of the underlying liver disease alone or a combination of the effects of thyrotoxicosis and the liver disease. The review focused on a literature search from the period January 2000 to June 2021 in the English language using MEDLINE via Ovid and EMBASE databases. Four random and relevant literature published before 2000 were included. Key search terms included hyperthyroidism, thyrotoxicosis, liver dysfunction, hepatitis and liver enzymes.

Putative Mechanisms for Liver Dysfunction in Hyperthyroidism

Several direct and indirect mechanisms have been suggested as the cause of liver dysfunction in hyperthyroidism. Summarily, these include direct liver toxicity from prolonged exposure to excessive thyroid hormones and hepatocyte anoxia with



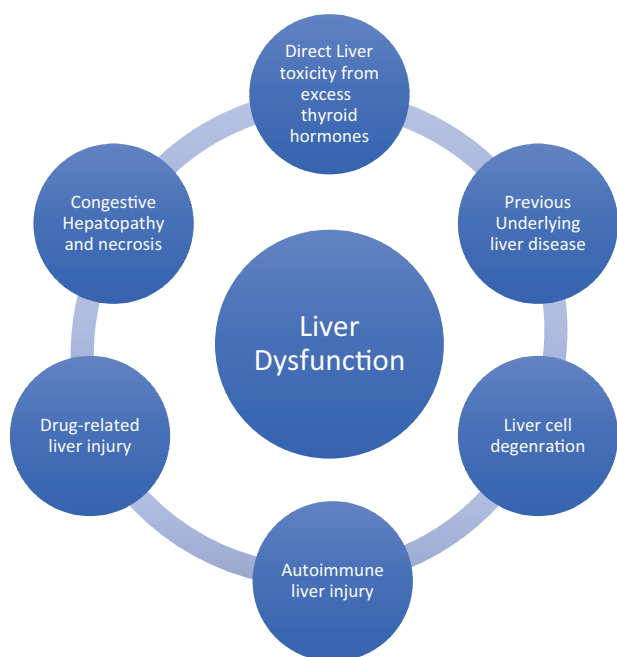


Figure 1. Mechanisms for liver dysfunction in hyperthyroidism.

free-radical damage as a result of the hypermetabolic state, liver cell degeneration from accelerated liver glycogen and protein decomposition, autoimmune-related liver injury, congestive hepatopathy (necrosis) from concomitant thyrotoxic heart failure, previous underlying liver disease and antithyroid medication-related liver toxicity and injury,^{1,11-14} refer Figure 1.

The pattern of liver dysfunction associated with hyperthyroidism vary. In situations without heart failure and underlying autoimmune causes, elevated aspartate amino transferase, and alanine aminotransferase (transaminitis) results from tissue ischemia and infarction of the hepatocytes. This is as a result of the increase in metabolic activity which increases oxygen demand by the liver.^{1,15-17} T₃ causes apoptosis through a mitochondrion-dependent pathway. Typical histological findings include fatty infiltration of the hepatocytes, nuclear irregularity, hyperchromatism in hepatocytes and vacuolization of the cytoplasm. Cholestatic pattern is commoner than synthetic liver dysfunction,¹⁸ and some may present with severe jaundice as the main presentation. Rises in ALP and GGT are seen about 64% and up to 62% of thyrotoxicosis cases respectively.^{19,20} In one series, elevations in serum ALP were followed in frequency by increases in levels of GGT, bilirubin, and aminotransferases.¹⁸ Elevation in ALP is due to increased osteoblastic activity and driven mainly by bone isoenzyme.²¹

Congestive heart failure may occur as a complication of hyperthyroidism (thyrotoxic heart failure) or as a preexisting condition. Whilst sinus tachycardia, atrial fibrillations are common manifestations, frank heart failure is uncommon without underlying pre-existing heart condition. In the series by Wafa et al²² only two patients with severe hepatic dysfunction had global heart failure. Heart failure usually results in mild abnormalities in liver dysfunction, however, acute congestion may lead to marked increases

in aminotransferases and bilirubin similar to values associated with viral and toxic hepatitis.^{16,23} In a recent publication involving 2 patients with Graves' disease, we found out that the liver dysfunction was a predominantly cholestatic pattern rather than transaminitis in the patient with thyrotoxic heart failure, whilst the second patient without heart failure had equivalent derangements in cholestasis and transaminitis.⁶ Generally, it is observed that patients with hyperthyroidism and heart failure exhibit more severe liver dysfunction (deep jaundice), hepatomegaly, ascites and coagulopathy than those without heart failure.^{15,16}

Graves' disease can occur concurrently with other autoimmune conditions in about 10 % of cases²⁴; common among these are primary biliary cirrhosis (PBC), autoimmune cholangiopathy (AIC) or autoimmune hepatitis. These autoimmune conditions usually have positive antinuclear antibody (ANA) and high ALP; AIC and some PBC cases are negative for anti-mitochondrial antibody (AMA).

It is often difficult to decide if the cause of hepatic dysfunction is due to antithyroid medications (thionamides) particularly if liver functions tests (LFTs) were not assessed before commencement of medications. It is estimated that the incidence of antithyroid associated hepatic dysfunction is between 0.1% and 0.2%²⁵; and risk factors for hepatic injury include older age and higher doses of antithyroid medications. In severe cases of liver dysfunction, the offending drugs should be withdrawn and consideration given to the use cholestyramine to improve cholestatic symptoms, whilst the underlying hyperthyroidism is definitively treated with radioiodine therapy or surgery.^{26,27}

Predictors of Liver Dysfunction and Recovery

So far, studies have not demonstrated a correlation between abnormal liver biochemical tests and thyroid hormone levels. Generally, there is normalization of liver dysfunction as thyroid hormone improves.^{6,22} Li et al²⁸ found out that among Graves' disease patients, higher thyroid hormone of free thyroxine (FT₄) >70.5 pmol/L with the heart rate above 90 beats per minute, the risk of hepatic function injury increases. Another study also found that hepatic abnormalities were greater in a cohort of 19 patients with hyperthyroidism and chronic heart failure (CHF).¹⁶ One study however showed a negative correlation between ALT and left ventricular ejection fraction (LVEF) among patients with thyrotoxicosis and heart failure.²²

Timely initiation of antithyroid medications lead to improvement in liver dysfunction^{6,22}; particularly when biochemical euthyroidism is attained. In a recent systematic review and meta-analysis, following the initiation of antithyroid medications and attainment of euthyroidism, there was normalization abnormalities in ALT, AST, ALP, BIL, and GGT in 83%, 87%, 53%, 50%, and 70% respectively.

Conclusion

Hepatic dysfunction associated with thyrotoxicosis is common finding in clinical practice. Whilst the exact mechanisms are unknown, both direct and indirect causes are involved. The

challenge is sometimes to establish the definitive factor causing liver injury in a particular patient. Examination of liver function in the setting of hyperthyroidism is important to identify any abnormalities; timely initiation of antithyroid medication generally results in improvement.

Author Contributions

EY conceived the study and its design, data search, analysis, drafted and produced the final manuscript.

ORCID iD

Ernest Yorke  <https://orcid.org/0000-0003-4257-7492>

Data Accessibility/Availability

The data used to support the findings of this study are available from the corresponding author upon request.

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